Color Doppler ultrasonography in full term neonates with hypoxic ischemic encephalopathy and prediction of outcome

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Abstract  Background: Impaired cerebral circulation plays the main role in the pathogenesis of hypoxic-ischemic brain injury in neonates. Objectives: We aimed to determine blood flow parameters via color Doppler ultrasonography in full-term neonates with hypoxic-ischemic (HI) brain injury at 12 h postpartum and the correlation of these parameters with long-term outcomes at the age of 1-year. Design and subjects: Our study included 40 full term neonates with HIE (Patients group) and 25 healthy full term neonates (control group). All neonates were subjected to early color Doppler ultrasonography. At the age of 1-year the neurodevelopmental condition was evaluated. Results: The end-diastolic velocity (EDV) and peak systolic velocity (PSV) values of cerebral arteries of patient group were significantly lower than those of the control group. Resistive index (RI) values were significantly higher in patient group than in the control group \((P < 0.05)\). The values obtained from right and left anterior and middle cerebral arteries of patients and controls were significantly correlated \((P < 0.05)\). During follow up of these cases, seven died in NICU, eleven were found to have neurodevelopmental sequelae and twenty-two were found to be normal. In comparison between neonates with good prognosis (No. 22) and those of poor prognosis (No. 18) in terms of EDV, PSV and RI retrospectively, we found EDV and PSV to be significantly lower and RI to be significantly higher \((P < 0.05)\). Conclusion: Detection of a decrease in cerebral blood flow in neonates in the first 12 h postpartum has a prognostic value.

Introduction

Perinatal asphyxia (PA) remains one of the main causes of mortality and morbidity among newborns, with an estimated incidence of 1-8 per 1000 live births according to different studies. The rapid advances in neonatal intensive care unit (NICU) have decreased the incidence of infants with adverse
neurodevelopmental outcomes; however, birth asphyxia is the major cause of hypoxic-ischemic brain injury in neonates born at term. It is important to assess the severity of asphyxia to give adequate treatments and prevent brain damage. In addition to imaging findings from computed tomography, magnetic resonance imaging, and spectroscopy, cerebral sonography in the neonatal period can provide an early guide to the neurodevelopmental prognosis. The Doppler technique is a noninvasive method that can be used at the bedside without disturbing patients. As survivors of severe hypoxic-ischemic encephalopathy (HIE) have profound long-term neurologic disability like cerebral palsy, mental retardation and epilepsy and a large majority of infants with moderate HIE have cognitive problems, sequelae of HIE require a significant resource. According to the recommendations of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, the measurements of resistive index (RI) and end diastolic flow velocity (EDFV) in the anterior cerebral artery are performed in order to assess cerebral perfusion and early predict an outcome. An increase in EDFV indicates local or diffuse vasodilatation, caused by increased pCO2 in case of asphyxia and accumulation of metabolites. However, in many countries, color Doppler ultrasonography (cD-USG) is not widely applied in daily practice, and data on its diagnostic and prognostic potential remain scarce. It has been proven that impaired cerebral circulation plays the main role in the pathogenesis of hypoxic-ischemic brain injury in neonates, yet studies conducted so far have been insufficient to explain how changes in blood circulation parameters are related to long-term outcomes.

**Aim of the work**

The aim of the study was to determine the role of blood flow parameters evaluated via color Doppler ultrasonography in postasphyxial full term neonates at 12 h and possible prognostic value.

**Patients and methods**

This prospective case-control study was conducted at the Neonatal intensive care unit (NICU), Menoufia University Hospital, Egypt from April 2012 to January 2014. The patient group consisted of 40 full-term (≥37 weeks of gestation) neonates who suffered from hypoxia or asphyxia during birth. The control group consisted of 25 healthy full-term neonates. Written informed consent was taken from their families for participation in the study.

**The inclusion criteria for the patient group neonates were as follows:**

Full-term (≥37 weeks of gestation) neonates born with perinatal hypoxia or asphyxia required resuscitation, Apgar score at 5 min after birth ≤6 points, fetal acidosis (umbilical artery blood pH < 7.2) or neonatal acidosis (capillary blood pH within the first hour after birth < 7.3).

**The exclusion criteria for the patient group neonates were as follows:**

Full-term (≥37 weeks of gestation) neonates with congenital developmental or chromosome abnormalities, hemolytic disease of the newborn, congenital brain infection or severe sepsis with hemodynamic disturbances, or suspected metabolic diseases.

**The inclusion criteria for the control group neonates were as follows:**

Full-term (≥37 weeks of gestation) neonates who did not require resuscitation, Apgar score on the first and the fifth minute of life ≥8 points, and no neonatal pathologies.

**The neurological status**

The neurological status was evaluated every day for the first three days of life. The HIE stage was evaluated using the modified Sarnat and Sarnat scale.

**Brain ultrasonography**

Using a digital ultrasound device Xario SSA-660A (Toshiba) with a sector 5–9 MHz transducer, and a linear 7–14 MHz transducer, every subject underwent brain scanning at 12 h postpartum. Brain structures were visualized using acoustic windows: the frontal, the occipital, the temporal, and the mastoid fontanelles. The brain was evaluated in different planes: anterior, posterior, lateral, diagonal, and axial planes.

**Doppler sonography**

Doppler sonography was conducted simultaneously with USG. In all subjects, cerebral blood flow parameters – peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) – were measured in the anterior cerebral arteries (the right and the left one) and the middle cerebral arteries (the right and the left one). Imaging of the anterior cerebral arteries was bilaterally conducted on the parasagittal planes, obtaining the image through the anterior fontanel. Blood flow velocity parameters in all subjects were measured in the branch of the anterior artery located in front of the genus of corpus callosum. Imaging of the medial cerebral arteries was bilaterally conducted through the right and the left temporal bones on axial planes, at the level of cerebral peduncles. Blood flow velocity parameters in all subjects were measured in the proximal branch of the medial cerebral artery, in the lateral sulcus (the fissure of Sylvius). We tried to keep the angle of insonation as close to 08 as possible (not more than 158). In total, 5 cardiac cycles were measured on spectrograms. The exposure time of intravascular Doppler sonography (DSG) was ≤60 s so as not to exceed the safety margin – 100 mW/cm². The neonates’ examination was performed at rest or during sleep.

After discharge of patient group from NICU, they were evaluated in the outpatient clinic for neurodevelopmental status by doing neurological examination and Denver Developmental screening test II.

**Denver developmental screening test II**

The Denver Developmental Screening Test II (DDST) was used to screen children’s development. Four areas (fine motor, gross motor, personal–social, and language) of functioning
were tested. It consists of 125 items, and the development of a child is measured based on these 125 items. The test usually takes 10–20 min to perform, and the child is classified as within normal range, suspect, or delayed based on the test results.15

Statistical analyses

Values are displayed as mean ± SD for quantitative variables or in number and percentage for qualitative parameters. Statistical analyses were made using Mann–Whitney U test and Pearson’s correlation analysis by the aid of SPSS statistical software (version 17.0, SPSS Inc., Chicago, IL, USA). P value of <0.05 was considered to be significant.16

Results

Patient group included 40 neonates with HIE, 23 were males and 17 were females. They were classified according to Sarnat clinical staging into grade I which included 7 neonates, grade II which included 18 neonates and grade III which included 15 neonates. Control group included 25 healthy neonates, 15 were males and 10 were females. The gestational ages, birth weight, heart rate, systolic arterial blood pressure, diastolic arterial blood pressure and application time of US showed no significant differences between patient and control groups (Table 1).

The EDV and PSV values obtained from right and left anterior and middle cerebral arteries of patient group were significantly lower than those of the control group. RI values were significantly higher in patient group than in the control group (P < 0.05) (Fig. 1). The values obtained from right and left anterior and middle cerebral arteries of patients and controls were significantly correlated (P < 0.05) (Table 2).

Cranial ultrasound findings in patient group showed 19 (48.5%) with no abnormal findings, 4 (10%) with intraventricular hemorrhage, 8 (20%) with increased periventricular density and 9 (22.5%) with increase in echodensity of cerebral parenchyma. US findings in control group are normal (Table 3).

After discharge of asphyxiated neonates from NICU, they were followed up for a mean duration of 11 ± 2.8 months in the outpatient clinic. Seven of asphyxiated neonates died in NICU, in the latter follow up of these cases, eleven of them were found to have neurodevelopmental sequelae and twenty-two were found to be normal. When we compared neonates with good prognosis (No. 22) with those of poor prognosis (No. 18) in terms of EDV, PSV and RI retrospectively, we found EDV and PSV to be significantly lower and RI to be significantly higher (P < 0.05) (Table 4).

Discussion

Prognostication of long-term outcomes is one of the main objectives in USG and Doppler sonography of the brain of full-term neonates who experienced PA. Our study analyzed how HI brain injury detected via USG during the first days of life is related to long-term (1-year after the birth) outcome. The principal mechanism of pathogenesis underlying most of the neuropathology attributed to intrapartum hypoxia–ischemia

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of studied groups.</th>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Control</td>
</tr>
<tr>
<td>(No. = 40)</td>
<td>(No. = 25)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.7 ± 0.704</td>
</tr>
<tr>
<td>Birth weight (gm)</td>
<td>3148 ± 103</td>
</tr>
<tr>
<td>Heart rate (b/min)</td>
<td>133 ± 17</td>
</tr>
<tr>
<td>Systolic arterial blood pressure (mmHg)</td>
<td>68.5 ± 4.7</td>
</tr>
<tr>
<td>Diastolic arterial blood pressure (mmHg)</td>
<td>35.2 ± 3.6</td>
</tr>
<tr>
<td>Application time of US (h)</td>
<td>9.5 ± 0.8</td>
</tr>
</tbody>
</table>

Figure 1 Color Doppler ultrasonography of cerebral artery of asphyxiated full term neonates showing decreased EDV and PSV and increased RI. EDV: End diastolic velocity, PSV: Peak systolic velocity, RI: Resistive index.
is impaired cerebral blood flow (CBF), which occurs most likely because of interruption in placental blood flow and gas exchange. However, the development of brain injury after hypoxia–ischemia is an evolving process which is initiated during the hypoxic-ischemic insult but extended into the reperfusion period during recovery. The brain damage, following hypoxic-ischemic insults, develops after a delay, being preceded by the symptom-free interval or even the temporary improvement of the clinical picture immediately after insult. In our study, we used cranial US to detect changes of HIE and exclude other causes of encephalopathy. We found 48.5% of patients with no abnormal findings, 10% with intraventricular hemorrhage, 20% with an increased periventricular density and 22.5% with an increase in echodensity of cerebral parenchyma. Our results are in concordance with other studies. In our study we used cD-USG to detect the pattern of blood flow velocity (BFV) in anterior and medial cerebral arteries as cD-USG is a non-invasive method, which allows repeated and safe assessment of hemodynamics in neonatal units. Several studies have demonstrated that the cD-USG technique can be used to examine the pattern of blood flow velocity (BFV) in the major vessels of the brain as well as visceral organs in neonates with good reproducibility. The BFV findings have clinical relevance in interpreting the cardiovascular adaptation of distressed newborn infants with a decompensation of circulatory responses and the possible development of multiorgan failure including brain damage.

In our study we found that EDV and PSV decreased in newborns with HIE in the first 12 h after birth whereas RI showed an increase. These findings indicate a decreasing CBF and an increasing blood vessel resistance in the post-asphyxia first 12 h. An increase in BFV during the first hours after birth indicates a normal reaction to the postnatal environment. Pezzati et al. evaluated CBF in the anterior and medial cerebral arteries of healthy preterm and full-term newborns (gestational age, 24–41 weeks) and showed that the BFV at 2–8 h after birth increased significantly with increasing gestational age and birth weight. Newborns with PA and HIE had significantly lower

### Table 2
Comparison of EDV, PSV and RI values between asphyxiated and normal neonates obtained from right and left anterior and middle cerebral arteries.

<table>
<thead>
<tr>
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<th>Right</th>
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<tbody>
<tr>
<td></td>
<td>Middle</td>
<td>Anterior</td>
<td>Middle</td>
<td>Anterior</td>
</tr>
<tr>
<td></td>
<td>RI</td>
<td>EDV</td>
<td>PSV</td>
<td>RI</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 40</td>
<td>0.74</td>
<td>± 0.03</td>
<td>5.6</td>
<td>± 0.85</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.65</td>
<td>± 0.03</td>
<td>8.2</td>
<td>± 1.25</td>
</tr>
<tr>
<td>n = 25</td>
<td>0.68</td>
<td>± 0.04</td>
<td>7.8</td>
<td>± 1.05</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.010</td>
<td>0.002</td>
<td>0.001</td>
<td>0.030</td>
</tr>
</tbody>
</table>

RI: resistive index, EDV: end diastolic velocity, PSV: peak systolic velocity.

### Table 3
Cranial ultrasound findings in patient group.

<table>
<thead>
<tr>
<th>Ultrasound findings</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>19(48.5)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>4(10)</td>
</tr>
<tr>
<td>Increased periventricular density</td>
<td>8(20)</td>
</tr>
<tr>
<td>General increase in echo density of cerebral parenchyma</td>
<td>9(22.5)</td>
</tr>
</tbody>
</table>

### Table 4
Comparison of PSV, EDV and RI values of neonates who have good and bad prognosis.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Middle</td>
<td>Anterior</td>
<td>Middle</td>
<td>Anterior</td>
</tr>
<tr>
<td></td>
<td>RI</td>
<td>EDV</td>
<td>PSV</td>
<td>RI</td>
</tr>
<tr>
<td>Good</td>
<td>0.71</td>
<td>± 0.03</td>
<td>6.4</td>
<td>± 0.78</td>
</tr>
<tr>
<td>No = 22</td>
<td>0.72</td>
<td>± 0.03</td>
<td>5.2</td>
<td>± 0.57</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bad</td>
<td>0.79</td>
<td>± 0.05</td>
<td>5.1</td>
<td>± 0.89</td>
</tr>
<tr>
<td>No = 18</td>
<td>0.82</td>
<td>± 0.06</td>
<td>4.6</td>
<td>± 0.52</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>0.042</td>
<td>0.031</td>
<td>0.022</td>
<td>0.030</td>
</tr>
</tbody>
</table>

RI: resistive index, EDV: end diastolic velocity, PSV: peak systolic velocity.

SD: standard deviation.
peak systolic flow velocity (PSFV) and EDFV in the anterior and medial cerebral arteries at 12 h of life as compared with control newborns (P < 0.05). Ilves et al. reported that cerebral blood flow velocities (PSFV and EDFV) measured up to 6 h after asphyxia are not specific and not suitable for the prediction of HIE severity and long-term unfavorable outcomes such as death and severe disability. At the age of 2–6 h, there was no significant difference in PSFV and EDFV between newborns with mild to moderate HIE and those with severe HIE. Moreover, no significant difference in PSFV and EDFV was found between newborns with a poor outcome (death or severe disability) and newborns with normal development/mild impairments. The evaluation of cerebral blood flow within 12 ± 2 h has a greater prognostic value. Cerebral blood flow velocities differ depending on the severity of HIE. Ilves et al. reported that increased blood flow velocities of more than 3 SD at the age of 12 ± 2 h showed an early onset of severe vasoparalysis of the brain and were found to be associated with severe HIE and unfavorable outcomes. The role of CBFV measured in postasphyxial period in predetermining a prospective prognosis has been investigated by many authors (Boo et al. 2000, Kirimi et al. 2002, Liu et al. 2007, Kudrevičienė et al. 2014). They reported that EDV, PSV and RI would be very useful in determining the prognosis of HIE. 28–31

In our patients, when comparing CBFV of 18 neonates with poor prognosis with other cases, they have been found to be flawed. Such findings together with numerous others by different authors show that the evaluation of CBFV during post asphyxia period of the infants would be of great importance in prediction of developmental prognosis of such cases with HIE. 32

In the study conducted by Kudrevičienė et al. 31 they analyzed the relationship of cerebral blood circulation parameters PSFV, EDFV and RI evaluated 12–24 h after birth with neuromotor and mental development of 1-year-old children. The study showed that subjects who on the first day were found to have significantly higher PSFV and EDFV values and lower RI values demonstrated severe impairment of mental development (P < 0.05). A number of researchers analyzed associations between blood flow parameters measured via cD-USG on the first days of life and long-term outcomes. Some researchers analyzed the significance of blood flow parameters measured during the first 12 h of life. They found that the accuracy indices of blood circulation parameters are low. That the accuracy of blood circulation parameters improved when the examination was performed in the second half of the first day and on subsequent days. Kirimi et al. investigated the relationship of blood flow parameters registered during the first 12 h after birth with neuromotor and mental development of 1-year-old children. They found that neonates whose PSFV and EDFV of cerebral blood flow were significantly lower, and R was significantly higher, were found to have cerebral palsy (CP) and impairment of the mental and neuromotor development. Ilves et al. found that in children with poor outcomes (death or marked disability), blood flow (PSFV and EDFV) values in the anterior and medial cerebral arteries recorded 12 h after birth was significantly higher than those in the control group. In children whose psychomotor development at the age of 18 months was unaltered or only slightly impaired, blood flow PSFV and EDFV values in the anterior and medial cerebral arteries recorded 12 h after birth were significantly lower than those in the group of healthy full-term neonates. Fukuda et al. in their study conducted in 2005 in Japan found that in subjects with PA followed by asymptomatic HIE, who at the age of 1-year were diagnosed with CP, CBF mean flow velocity (Vm) on the first day after birth was significantly lower (ischemia) than in subjects without HIE or CP. According to the researchers, a higher Vm in subjects with HIE resulted from unstable hemodynamics, and a low Vm in the absence of clinical signs of HIE allows for prognosticating long-term outcomes.

Conclusion

Cerebral blood flow parameters evaluated via Doppler sonography are of great importance in evaluating CBFV in neonates with HIE. Detection of a decrease in CBFV in neonates in the first 12 h postpartum has a prognostic value.

Conflict of interest

None.

References

Color Doppler Ultrasonography in hypoxic ischemic encephalopathy


